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Herbal medicines for the treatment of acute otitis media: Protocol for a systematic review

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Article focus

- The aim of this systematic review is to analyze the trial data on the effectiveness of herbal medicines for acute otitis media.

Key messages

- This systematic review will be performed with a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.

Abstract

Introduction: The aim of this systematic review is to analyze the trial data on the effectiveness of herbal medicines for acute otitis media.

Methods and analysis: The following eleven databases will be searched from their inception: MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Allied and Complementary Medicine Database (AMED), the Cochrane Central Register of Controlled Trials (CENTRAL), China Network Knowledge Infrastructure (CNKI) and five Korean databases [Oriental Medicine Advanced Searching Integrated System (OASIS), DBPIA, KoreaMed, Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)]. The selection of the studies, the data abstraction, and the validations will be performed independently by two researchers.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013:CRD42013004836.

Introduction

Description of the condition

Acute otitis media (AOM) is one of the most common childhood infections and has a high morbidity and low mortality. More than 80% of children experience AOM at least once, and one in three have more than three episodes. According to the 2006 Health Medical Expenditure Panel Survey data, the yearly cost of AOM was $2.8 billion.[1-3] AOM is caused by bacterial infections, and the prevalence of nasopharyngeal colonization by organisms such as *Streptococcus pneumoniae*, *Moraxella catarrhalis* and non-typeable *Haemophilus influenzae* is strongly related to AOM. [4] AOM is defined as the presence of middle-ear effusion and the rapid onset of one or more signs or symptoms of middle-ear inflammation, such as an earache, ear rubbing, a bulging eardrum, or fever.[5] AOM can progress to recurrent AOM or otitis media with effusion (OME) and thereby cause high socioeconomic costs. [6]

Description of the intervention

The majority of patients with AOM are treated with antibiotics, and AOM is the most prevalent reason for children to take antibiotics. However, antibiotics have been suggested to provide only a marginal benefit and are not adequately effective for the relief of pain and distress. [7 8] A review of randomized controlled trials involving the treatment of AOM with antibiotics revealed a limited role for antibiotics, and 80% of the untreated children were pain-free between 2 and 7 days after the onset of AOM. [9 10] The literature regarding AOM recommends a watchful waiting approach in many cases. [11]

How the intervention might work

In recent years, a large number of AOM patients have chosen complementary and alternative medicine (CAM) to cure or prevent AOM. [12] Forty-six percent of children with recurrent

AOM used some component of CAM, [13] and herbal medicine is approved by the World Health Organization as a therapy for the treatment of AOM. [14 15]

Herbal medicine is a therapy that utilizes medicinal plants, minerals and animal parts to prevent or cure clinical conditions. Many types of herbal medicines have an anti-inflammatory effect and an immunomodulatory function, such as increasing phagocytosis. [16-18] Experimental research on otitis media has indicated that herbal medicines reduce swelling and prevent endotoxin-induced otitis media. [19 20] In a clinical study, Jusen-taiho-to found a decrease in both hospital visits and the use of antibiotics in AOM patients. [17].

Why it is important to do this review

However, to our knowledge, no systematic reviews assessing the intervention of herbal drugs in AOM have been conducted to date despite this increasing use of CAM. A comprehensive evaluation of the effectiveness and safety of herbal drugs will inform the recommendation for patients to use an herbal drug treatment.

Objectives

Therefore, we will undertake a systematic review to assess the safety and efficacy of herbal drugs for the treatment of AOM.

Methods

Criteria for considering studies for this review

Types of studies

Studies with the following study designs will be included:

1. Randomized controlled trials, including cluster randomized trials,

2. Quasi-randomized trials, in which group allocation is not purely random but may be determined by a factor such as a birth date, a hospital record number or alternation.

Any trials without parallel comparisons or control groups will be excluded.

Types of participants

Patients suffering from AOM, without ventilation tubes, will be included. The diagnostic criteria for AOM should be based on the criteria of the World Health Organization, The American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS), but if necessary, trials with a definition of AOM used by the authors of the trial in question will be included.

Types of interventions

We will include those trials with herbal medicine used alone or as a combined therapy of herbal medicine with a conventional therapy versus the same conventional therapy. Herbal medicine is defined as a single herb, an individually prescribed herbal formula and herbal products extracted from natural herbs. There is no limitation on the number of herbs used, the dosage, the forms of medication or the duration of the treatment. We will only include the oral administration of medication.

Types of outcome measures

Primary Outcome

1. Proportion of patients with pain or intensity of pain

2. Proportion of patients with fever or intensity of fever

3. Proportion of patients with pain and fever or intensity of pain and fever

Secondary Outcome

If possible, the following will be reviewed:

1. Abnormal tympanometry findings at various time points (four to six weeks and three months) as a surrogate measure for hearing problems caused by middle-ear fluid

2. Tympanic membrane perforation

3. Contralateral otitis (in unilateral cases)

4. AOM recurrences

5. Serious complications related to AOM, such as mastoiditis and meningitis

6. Adverse effects likely to be related to herbal medicine

7. Quality of life

8. Duration of remission

Search methods for the identification of studies

Electronic searches

We will search for trials contained in the following electronic databases: MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Allied and Complementary Medicine Database (AMED) and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also search one Chinese database [China Network Knowledge Infrastructure (CNKI)] and five Korean databases [Oriental Medicine Advanced

Searching Integrated System (OASIS), DBPIA, KoreaMed, Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)].

Searching other resources

We will also check the reference lists of reviews and the retrieved articles for additional studies. We will search the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct), Clinical trials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials.

Search strategy

Search strategies for The Cochrane Library, MEDLINE, and EMBASE are presented in Appendix 1. These strategies will be modified for use in other databases.

Data collection and analysis

Selection of studies

Two review authors (Son MJ and Kim YH) will independently screen the titles and abstracts of the searched studies, perform the study selection and record their decisions on a standard eligibility form. When disagreements regarding the study selection are not resolved through discussions between these two authors, the arbiter (Lee MS) will decide.

Inclusion Criteria

1. In randomized cross-over trials, only the data from the first period will be included because of the carry-over effect

2. No language limitation

3. No publication status restriction

Exclusion Criteria

1. Animal experiments

2. Non-randomized clinical trials

3. Case report/series, news items, and letters

4. Qualitative studies

Data extraction and management

Two review authors (Son MJ and Kim YH) will read hard copies of all the articles and independently extract the data using a standard data extraction form. Any disagreement between the authors will be resolved by a discussion with all the authors. When the reported data are insufficient or ambiguous, the authors (Kim YH and Lee HW) will contact the corresponding clinical trial authors by e-mail or telephone to request additional information or clarification.

Assessment of risk of bias in the included studies

We will independently assess the risk of bias in the included studies according to the criteria from the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[21] The quality of each trial will be categorized into a low, unclear or high risk of bias. If necessary, we will contact the authors of the assessed trials for clarification. We will resolve any differences in opinion through discussion or consultation with a third author.

Measurement of the treatment effect

For the continuous data, we will use the mean difference (MD) with 95% confidence intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present treatment effects as a relative risk (RR) with 95% CIs. We will convert other binary data into the RR form.

Units of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine the data from each control group. Subgroup analyses of the control groups will also be performed. Each patient will be counted only once in the analysis.

Dealing with missing data

Intention-to-treat analyses that include all the randomized patients will be performed. In the case of patients with missing outcome data, a carry-forward of the last observed response will be used. The individual patient data will be sought from the original source or from the published trial reports when the individual patient data are unavailable.

Assessment of heterogeneity

Clinically, various types of modalities and doses are included in herbal medicine treatments. We will use the random-effects model for the meta-analysis. If a meta-analysis is possible, we will use the I^2 statistic for quantifying the inconsistencies among the included studies. According to the guidance given in *the Cochrane Handbook* for Systematic Reviews of Interventions, 50% will be the cut-off point for meaningful heterogeneity. If heterogeneity is observed, we will conduct subgroup analysis to explore the possible causes. [22]

Assessment of reporting biases

If a sufficient number of included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[23] However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity of the included studies. [23 24]

Data synthesis

The differences between the intervention and the control groups will be assessed. RR and 95% CIs will be assessed for the effect size of each included study. All of the statistical analyses will be conducted using the Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.0 for Windows. For studies with insufficient information, we will contact the primary authors to acquire and verify data when possible. The chi-squared test and the I-squared test will be used to evaluate the heterogeneity of the included studies. Unless excessive statistical heterogeneity is present, we will then pool the data across studies for a meta-analysis using a random effects model.

Subgroup analysis and the investigation of heterogeneity

If there are an adequate number of studies, we will conduct subgroup analyses to interpret the heterogeneity between the studies, including the following:

1. Type of herbal medicine
2. Type of control
3. Type of age group.

Sensitivity analysis

If a sufficient number of studies are available, sensitivity analyses will be conducted to determine whether the findings are robust.

1. Sample size (e.g., more or less than 30 participants in each group)

2. Methodological qualities (e.g., allocation concealment or the blinding of participants/assessors)

3. Analysis-related issues (e.g., processes to handle missing data)

Discussion

Because no primary data collection will be undertaken, no additional formal ethical assessment or informed consent is required. The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Contributors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

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Conflicts of interest

None known

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Appendix 1. Search strategies

The Cochrane Library (Wiley Online Library)

#1	otitis media
#2	glue ear
#3	AOM
#4	middle ear infect*
#5	middle ear inflam*
#6	#1 or #2 or #3 or #4 or #5
#7	Medicine, Traditional
#8	Medicine, Arabic
#9	Medicine, Unani
#10	Medicine, East Asian Traditional
#11	Medicine, Chinese Traditional
#12	Medicine, Kampo
#13	Medicine, Ayurvedic
#14	Medicine, Korean Traditional
#15	Medicine, Mongolian Traditional
#16	Medicine, Tibetan Traditional
#17	Medicine, African Traditional
#18	phytotherapy
#19	ethnopharmacology
#20	ethnobotany
#21	Plant*
#22	Plants, Medicinal

#23	Plant Extract*
#24	Herbal Medicine
#25	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#6 and #25

PubMed

#1	Otitis Media
#2	glue ear
#3	AOM
#4	middle ear infect*
#5	middle ear inflam*
#6	or/1-5
#7	Medicine, African Traditional [mh]
#8	Medicine, Arabic [mh]
#9	Medicine, Ayurvedic [mh]
#10	Medicine, Kampo [mh]
#11	Medicine, Korean Traditional [mh]
#12	Medicine, Tibetan Traditional [mh]
#13	Medicine, Mongolian Traditional [mh]
#14	Herbal Medicine [mh]
#15	Phytotherapy [mh]
#16	Drugs, Chinese Herbal [mh]
#17	Plants, Medicinal [mh]

#18	Plant Extracts [mh]
#19	Ethnobotany [mh]
#20	Ethnopharmacology [mh]
#21	Plants [mh]
#22	herb* [tiab]
#23	or/7-22
#24	6 and 23

EMBASE

#1	'otitis'/exp AND media
#2	'glue'/exp AND 'ear'/exp
#3	AOM
#4	middle AND ('ear'/exp OR ear) AND infect*
#5	middle AND ('ear'/exp OR ear) AND inflam*
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	'african medicine'/exp OR 'african medicine'
#8	'korean medicine'/exp OR 'korean medicine'
#9	latin AND american AND ('medicine'/exp OR medicine)
#10	'chinese medicine'/exp OR 'chinese medicine'
#11	'oriental medicine'/exp OR 'oriental medicine'
#12	'mongolian medicine'/exp OR 'mongolian medicine'
#13	'tibetan medicine'/exp OR 'tibetan medicine'
#14	'traditional medicine'/exp OR 'traditional medicine'

#15	'herbal medicine'/exp OR 'herbal medicine'
#16	'ayurveda'/exp OR ayurveda
#17	'kampo'/exp OR kampo
#18	'phytotherapy'/exp OR phytotherapy
#19	'medicinal plant'/exp OR 'medicinal plant'
#20	'herbaceous agent'/exp OR 'herbaceous agent'
#21	'plant extract'/exp OR 'plant extract'
#22	'ethnobotany'/exp OR ethnobotany
#23	'ethnopharmacology'/exp OR ethnopharmacology
#24	'plant'/exp OR plant
#25	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26	#6 AND #25

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Abstract

Introduction: The aim of this systematic review is to analyze the trial data on the efficacy of herbal medicines for acute otitis media.

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Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013:CRD42013005100.

Article focus

- The aim of this systematic review is to analyze the trial data on the efficacy of herbal medicines for acute otitis media.

Key messages

- This systematic review will be performed with a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.

Introduction

Description of the condition

Acute otitis media (AOM) is one of the most common childhood infections and has a high morbidity and low mortality. More than 80% of children experience AOM at least once, and one in three have more than three episodes. AOM has high socioeconomic costs because it is the most common cause of physicians' visits and is a frequent diagnosis in prescribing antibiotics for children. AOM indirectly causes the loss of children's time and caregivers' working time and income, in addition to the medical costs. According to the 2006 Health Medical Expenditure Panel Survey data, the yearly cost of AOM was about $2.8- 3.8 billion.[1-4] AOM is caused by bacterial infections, and the prevalence of nasopharyngeal colonization by organisms such as *Streptococcus pneumoniae*, *Moraxella catarrhalis* and non-typeable *Haemophilus influenzae* is strongly related to AOM.[5] AOM is defined as the presence of middle-ear effusion and the rapid onset of one or more signs or symptoms of middle-ear inflammation, such as an earache, ear rubbing, a bulging eardrum, or fever.[6] AOM can progress to recurrent AOM, otitis media with effusion (OME) or conditions that are more serious, such as mastoiditis, meningitis, cerebritis or sigmoid sinus thrombosis.[7 8]

Description of the intervention

Although the majority of patients with AOM are treated with antibiotics, antibiotics have been suggested to provide only a marginal benefit and are not adequately effective for the relief of pain and distress.[9 10] A review of randomized controlled trials involving the treatment of AOM with antibiotics revealed a limited role for antibiotics, and 80% of the untreated children were pain-free between 2 and 7 days after the onset of AOM.[11 12]

In recent years, a large number of AOM patients have chosen complementary and alternative medicine (CAM) to cure or prevent AOM.[13] Forty-six percent of children with recurrent

AOM used some component of CAM such as herbal medicines.[14] Herbal medicine is a therapy that utilizes medicinal plants, minerals and animal parts to prevent or cure clinical conditions; it is approved by the World Health Organization as a therapy for the treatment of AOM.[15 16]

How the intervention might work

Herbal medicines reduce swelling and prevent endotoxin-induced otitis media by stimulating the function of the mucociliary system related to pathogen clearance in experimental research. [17 18] Also, many types of herbal medicines have anti-inflammatory and anti-bacterial effects, such as increasing phagocytosis for clearing up infection.[8 19-21] However, it is unclear how they work, in spite of observed immunomodulatory properties.

Why it is important to do this review

However, to our knowledge, no systematic reviews assessing the intervention of herbal drugs in AOM have been conducted to date despite this increasing use of CAM. A comprehensive evaluation of the efficacy and safety of herbal drugs will inform the recommendation for patients to use an herbal drug treatment.

Objectives

Therefore, we will undertake a systematic review to assess the safety and efficacy of herbal drugs for the treatment of AOM.

Methods

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Types of studies

Studies with the following study designs will be included:

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Patients suffering from AOM, without ventilation tubes, will be included. The diagnostic criteria for AOM should be based on the criteria of the World Health Organization, The American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS), but if necessary, trials with a definition of AOM used by the authors of the trial in question will be included.

Types of interventions

We will include those trials with herbal medicine used alone or as a combined therapy of herbal medicine with a conventional therapy versus the same conventional therapy. Herbal medicine is defined as a single herb, an individually prescribed herbal formula and herbal products extracted from natural herbs. There is no limitation on the number of herbs used, the dosage, the forms of medication or the duration of the treatment. We will only include the oral administration of medication. Conventional therapy would include the usual medication such as antibiotic drugs, decongestants, antihistamines and topical analgesia. Surgery, however, would be excluded.

Types of outcome measures

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1. Proportion of patients with pain or intensity of pain

2. Proportion of patients with fever or intensity of fever

3. Proportion of patients with pain and fever or intensity of pain and fever

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If possible, the following will be reviewed:

1. Abnormal tympanometry findings at various time points (four to six weeks and three months) as a surrogate measure for hearing problems caused by middle-ear fluid

2. Tympanic membrane perforation

3. Contralateral otitis (in unilateral cases)

4. AOM recurrences

5. Serious complications related to AOM, such as mastoiditis and meningitis

6. Adverse effects likely to be related to herbal medicine

7. Quality of life

8. Duration of remission

Search methods for the identification of studies

Electronic searches

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Knowledge Infrastructure (CNKI)] and five Korean databases [Oriental Medicine Advanced Searching Integrated System (OASIS), DBPIA, KoreaMed, Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)].

Searching other resources

We will also check the reference lists of reviews and the retrieved articles for additional studies. We will search the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct), Clinical trials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials.

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1. Randomized controlled trials and Quasi-randomized trials.

2. No language limitation

3. No publication status restriction

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2. Non-randomized clinical trials

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We will independently assess the risk of bias in the included studies according to the criteria from the Cochrane Handbook version 5.1.0, which include random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. [22] The quality of each trial will be categorized into a low, unclear or high risk of bias. If necessary, we will contact the authors of the assessed trials for clarification. We will resolve any differences in opinion through discussion or consultation with a third author.

Measurement of the treatment effect

For the continuous data, we will use the mean difference (MD) with 95% confidence intervals (CIs) to measure the treatment effect. We will convert other forms of data into MDs. In the case of outcome variables with different scales, we will use the standard mean difference (SMD) with 95% CIs. For dichotomous data, we will present treatment effects as a relative risk (RR) with 95% CIs. We will convert other binary data into the RR form.

Units of analysis issues

For cross-over trials, data from the first treatment period will be used. For trials in which more than one control group was assessed, the primary analysis will combine the data from each control group. Subgroup analyses of the control groups will also be performed. Each patient will be counted only once in the analysis.

Dealing with missing data

Intention-to-treat analyses that include all the randomized patients will be performed. In the case of patients with missing outcome data, a carry-forward of the last observed response will be used. The individual patient data will be sought from the original source or from the published trial reports when the individual patient data are unavailable.

Assessment of heterogeneity

Clinically, various types of modalities and doses are included in herbal medicine treatments. We will use the random-effects model for the meta-analysis. If a meta-analysis is possible, we will use the I^2 statistic for quantifying the inconsistencies among the included studies. According to the guidance given in *the Cochrane Handbook* for Systematic Reviews of Interventions, 50% will be the cut-off point for meaningful heterogeneity. If heterogeneity is observed, we will conduct subgroup analysis to explore the possible causes. [23]

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If a sufficient number of included studies (at least 10 trials) are available, we will use funnel plots to detect reporting biases.[24] However, funnel plot asymmetry is not the same as publication bias; therefore, we will attempt to distinguish the different possible reasons for the asymmetry, such as small-study effects, poor methodological quality and true heterogeneity of the included studies. [24 25]

Data synthesis

The differences between the intervention and the control groups will be assessed. RR and 95% CIs will be assessed for the effect size of each included study. All of the statistical analyses will be conducted using the Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.2.6 for Windows. For studies with insufficient information, we will contact the primary authors to acquire and verify data when possible. The chi-squared test and the I-squared test will be used to evaluate the heterogeneity of the included studies. Unless excessive statistical heterogeneity is present, we will then pool the data across studies for a meta-analysis using a random effects model.

Subgroup analysis and the investigation of heterogeneity

If there are an adequate number of studies, we will conduct subgroup analyses to interpret the heterogeneity between the studies, including the following:

1. Type of intervention

- type of herbal medicines

- existence of co-treatment e.g. herbal medicine used alone or as a combined therapy of herbal medicine with a conventional therapy

- the dose of herbal medicine

2. Type of design

- RCT or quasi RCT

3. Type of control

4. Type of age group

Sensitivity analysis

If a sufficient number of studies are available, sensitivity analyses will be conducted to determine whether the findings are robust.

1. Sample size (e.g., more or less than 30 participants in each group)

2. Methodological qualities (e.g., allocation concealment or the blinding of participants/assessors)

3. Analysis-related issues (e.g., processes to handle missing data)

Discussion

Because no primary data collection will be undertaken, no additional formal ethical assessment or informed consent is required. The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Contributors

The protocol was drafted by all authors. It was revised and the final version approved by all authors.

Funding

No external funding was received. Son MJ was supported by Korea Institute of Oriental Medicine (K13380), Kim YH and Lee HW were supported by same institute (K13101) and Lee MS was supported by same institute (K13400).

Conflicts of interest

None known

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Herbal medicines for the treatment of acute otitis media: Protocol for a systematic review

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License statement

Article focus

- The aim of this systematic review is to analyze the trial data on the efficacy of herbal medicines for acute otitis media.

Key messages

- This systematic review will be performed with a comprehensive search strategy and will establish the current status of the evidence with unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening and data extraction will be conducted independently by two authors.

Abstract

Introduction: The aim of this systematic review is to analyze the trial data on the efficacy of herbal medicines for acute otitis media.

Methods and analysis: The following eleven databases will be searched from their inception: MEDLINE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, Allied and Complementary Medicine Database (AMED), the Cochrane Central Register of Controlled Trials (CENTRAL), China Network Knowledge Infrastructure (CNKI) and five Korean databases [Oriental Medicine Advanced Searching Integrated System (OASIS), DBPIA, KoreaMed, Research Information Service System (RISS) and the Korean Studies Information Service System (KISS)]. The selection of the studies, the data abstraction, and the validations will be performed independently by two researchers.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2013:CRD42013005100.

Introduction

Description of the condition

Acute otitis media (AOM) is one of the most common childhood infections and has a high morbidity and low mortality. More than 80% of children experience AOM at least once, and one in three have more than three episodes. AOM has high socioeconomic costs because it is the most common cause of physicians' visits and is a frequent diagnosis in prescribing antibiotics for children. AOM indirectly causes the loss of children's time and caregivers' working time and income, in addition to the medical costs. According to the 2006 Health Medical Expenditure Panel Survey data, the yearly cost of AOM was about $2.8- 3.8 billion.[1-4] AOM is caused by bacterial infections, and the prevalence of nasopharyngeal colonization by organisms such as *Streptococcus pneumoniae*, *Moraxella catarrhalis* and non-typeable *Haemophilus influenzae* is strongly related to AOM.[5] AOM is defined as the presence of middle-ear effusion and the rapid onset of one or more signs or symptoms of middle-ear inflammation, such as an earache, ear rubbing, a bulging eardrum, or fever.[6] AOM can progress to recurrent AOM, otitis media with effusion (OME) or conditions that are more serious, such as mastoiditis, meningitis, cerebritis or sigmoid sinus thrombosis.[7 8]

Description of the intervention

Although the majority of patients with AOM are treated with antibiotics, antibiotics have been suggested to provide only a marginal benefit and are not adequately effective for the relief of pain and distress.[9 10] A review of randomized controlled trials involving the treatment of AOM with antibiotics revealed a limited role for antibiotics, and 80% of the untreated children were pain-free between 2 and 7 days after the onset of AOM.[11 12]

In recent years, a large number of AOM patients have chosen complementary and alternative medicine (CAM) to cure or prevent AOM.[13] Forty-six percent of children with recurrent

AOM used some component of CAM such as herbal medicines.[14] Herbal medicine is a therapy that utilizes medicinal plants, minerals and animal parts to prevent or cure clinical conditions; it is approved by the World Health Organization as a therapy for the treatment of AOM.[15 16]

How the intervention might work

Herbal medicines reduce swelling and prevent endotoxin-induced otitis media by stimulating the function of the mucociliary system related to pathogen clearance in experimental research. [17 18] Also, many types of herbal medicines have anti-inflammatory and anti-bacterial effects, such as increasing phagocytosis for clearing up infection.[8 19-21] However, it is unclear how they work, in spite of observed immunomodulatory properties.

Why it is important to do this review

However, to our knowledge, no systematic reviews assessing the intervention of herbal drugs in AOM have been conducted to date despite this increasing use of CAM. A comprehensive evaluation of the efficacy and safety of herbal drugs will inform the recommendation for patients to use an herbal drug treatment.

Objectives

Therefore, we will undertake a systematic review to assess the safety and efficacy of herbal drugs for the treatment of AOM.

Methods

Criteria for considering studies for this review

Types of studies

Studies with the following study designs will be included:

1. Randomized controlled trials, including cluster randomized trials,

2. Quasi-randomized trials, in which group allocation is not purely random but may be determined by a factor such as a birth date, a hospital record number or alternation.

Any trials without parallel comparisons or control groups will be excluded.

Types of participants

Patients suffering from AOM, without ventilation tubes, will be included. The diagnostic criteria for AOM should be based on the criteria of the World Health Organization, The American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS), but if necessary, trials with a definition of AOM used by the authors of the trial in question will be included.

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Appendix 1. Search strategies

The Cochrane Library (Wiley Online Library)

#1	otitis media
#2	glue ear
#3	AOM
#4	middle ear infect*
#5	middle ear inflam*
#6	#1 or #2 or #3 or #4 or #5
#7	Medicine, Traditional
#8	Medicine, Arabic
#9	Medicine, Unani
#10	Medicine, East Asian Traditional
#11	Medicine, Chinese Traditional
#12	Medicine, Kampo
#13	Medicine, Ayurvedic
#14	Medicine, Korean Traditional
#15	Medicine, Mongolian Traditional
#16	Medicine, Tibetan Traditional
#17	Medicine, African Traditional
#18	phytotherapy
#19	ethnopharmacology
#20	ethnobotany
#21	Plant*
#22	Plants, Medicinal

#23	Plant Extract*
#24	Herbal Medicine
#25	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#6 and #25

PubMed

#1	Otitis Media
#2	glue ear
#3	AOM
#4	middle ear infect*
#5	middle ear inflam*
#6	or/1-5
#7	Medicine, African Traditional [mh]
#8	Medicine, Arabic [mh]
#9	Medicine, Ayurvedic [mh]
#10	Medicine, Kampo [mh]
#11	Medicine, Korean Traditional [mh]
#12	Medicine, Tibetan Traditional [mh]
#13	Medicine, Mongolian Traditional [mh]
#14	Herbal Medicine [mh]
#15	Phytotherapy [mh]
#16	Drugs, Chinese Herbal [mh]
#17	Plants, Medicinal [mh]

#18	Plant Extracts [mh]
#19	Ethnobotany [mh]
#20	Ethnopharmacology [mh]
#21	Plants [mh]
#22	herb* [tiab]
#23	or/7-22
#24	6 and 23

EMBASE

#1	'otitis'/exp AND media
#2	'glue'/exp AND 'ear'/exp
#3	AOM
#4	middle AND ('ear'/exp OR ear) AND infect*
#5	middle AND ('ear'/exp OR ear) AND inflam*
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	'african medicine'/exp OR 'african medicine'
#8	'korean medicine'/exp OR 'korean medicine'
#9	latin AND american AND ('medicine'/exp OR medicine)
#10	'chinese medicine'/exp OR 'chinese medicine'
#11	'oriental medicine'/exp OR 'oriental medicine'
#12	'mongolian medicine'/exp OR 'mongolian medicine'
#13	'tibetan medicine'/exp OR 'tibetan medicine'
#14	'traditional medicine'/exp OR 'traditional medicine'

#15	'herbal medicine'/exp OR 'herbal medicine'
#16	'ayurveda'/exp OR ayurveda
#17	'kampo'/exp OR kampo
#18	'phytotherapy'/exp OR phytotherapy
#19	'medicinal plant'/exp OR 'medicinal plant'
#20	'herbaceous agent'/exp OR 'herbaceous agent'
#21	'plant extract'/exp OR 'plant extract'
#22	'ethnobotany'/exp OR ethnobotany
#23	'ethnopharmacology'/exp OR ethnopharmacology
#24	'plant'/exp OR plant
#25	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26	#6 AND #25